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EXAMINER	
LIETO, LOUIS D	

ART UNIT	PAPER NUMBER
1632	

DATE MAILED: 11/21/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/776,780	DURING, MATTHEW J.	
	Examiner	Art Unit	
	Louis D. Lieto	1632	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on _____.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-19* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-19* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *10 February 2004* is/are: a)☐ accepted or b)☒ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *3/19/04*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Claims 1-19 are pending and under examination.

Drawings

The drawings are objected to under 37 CFR 1.83(a) because they fail to show the histological details as described in the specification. Specifically, the resolution and clarity of figures 2-4, 7-10, 13, 16 and 17 are so poor as to make it impossible to discern the structural details. Corrected drawing sheets are required in reply to the Office action to avoid abandonment of the application. Any amended replacement drawing sheet should include all of the figures appearing on the immediate prior version of the sheet, even if only one figure is being amended. The figure or figure number of an amended drawing should not be labeled as "amended." If a drawing figure is to be canceled, the appropriate figure must be removed from the replacement sheet, and where necessary, the remaining figures must be renumbered and appropriate changes made to the brief description of the several views of the drawings for consistency. Additional replacement sheets may be necessary to show the renumbering of the remaining figures. The replacement sheet(s) should be labeled "Replacement Sheet" in the page header (as per 37 CFR 1.84(c)) so as not to obstruct any portion of the drawing figures. If the examiner does not accept the changes, the applicant will be notified and informed of any required corrective action in the next Office action. The objection to the drawings will not be held in abeyance.

Specification

The disclosure is objected to because of the following informalities:

1. The use of the trademarks NEUROBASAL (pg 47, line 1), MINI COMPLETE (pg 49, line 26) has been noted in this application. They should be capitalized wherever they appears and be accompanied by the generic terminology. Although the use of trademarks is permissible in patent applications, the proprietary nature of the marks should be respected and every effort made to prevent their use in any manner that might adversely affect their validity as trademarks.

2. The Brief Description of Drawings refers to Figures 2A-2H, but there is no description of Figures 2E-2H.

3. The Brief Description of Drawings refers to a bar chart in Figure 6H, but the bars in Drawing 614 are not labeled and it cannot be determined which bars represent which animals.

4. The Brief Description of Drawings refers to two line graphs in Figures 7A-7B, but the various lines that represent different animal groups in Drawings 7A-7B cannot be differentiated between one another. The Description refers to one line being dashed and one line being solid, but both lines are solid.

5. The Brief Description of Drawings refers to different rat groups in Figures 12A- 12D, but it cannot be determined which lines and bars represent each particular rat group in Drawings 12A-12D.

Appropriate correction is required.

Claim Objections

Claim 5 is objected to because of the following informalities: Stroke is misspelled as "Stoke". Appropriate correction is required.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1,2,5-12, and 15-19 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claims contain subject matter that was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Claims 1,2,5-12, and 15-19 are drawn to a neurological vaccine comprising a vector encoding any neuroreceptor antigen for treatment of any injury, disease or excessive neurological activity and methods of using the vaccine. The claims encompass a vast genus of vaccines encoding neuroreceptor antigen, defined solely by their ability to be expressed and to raise an antibody response. The claims are drawn to a genus of vaccines for the treatment of any neurological disorder, including any injury, including blunt force trauma, and any excessive neurological activity.

To provide adequate written description and evidence of possession of a claimed genus, the specification must provide sufficient distinguishing identifying characteristics of the genus. The factors to be considered include disclosure of complete or partial structure, physical and/or chemical properties, functional characteristics, structure/function correlation, methods of making the claimed product, or any combination thereof. In this case, the specification only contemplates a subset of neurotransmitter receptors, such as: "N-methyl-D-aspartate (NMDA) receptor, neuronal glutamate receptors (GluR's), γ-aminobutyric acid receptors (GABAR'S),

nicotinic acetylcholine receptors, serotonin receptors, dopamine receptors, and the like." (Specification pg. 16, lines 15-20). However, the term neuroreceptor is broad enough to include interleukin receptors. Further, the specification defines a neurological disorder as any impairment or absence of a normal neurological function or presence of an abnormal neurological function in a subject (Specification, pg. 10, lines 25-32). This would include at least death (the absence of normal neurological function), insanity (impairment), and schizophrenia (abnormal function). However, the specification does not contemplate the receptors and the cells to be targeted in "neurological disorders" such as death, insanity, or schizophrenia. The specification does not contemplate any vaccine for treating these disorders. Finally, the specification does not contemplate any receptors that can be used as the basis of said vaccine to immunize against the damage sustained from injuries such as blunt force trauma. While the claims limit the vaccines to antigens that can induce an antibody response, any antigen expressed at sufficient levels in a subject with a normal immune system can induce an antibody response.

There is no identification of any particular portion of any neuroreceptor antigen that must be conserved. The specification does not state that any functional domains or motifs, or characteristics must be conserved between the neuroreceptor antigens in order to function as vaccine. Accordingly, in the absence of sufficient recitation of a distinguishing identifying characteristic, the specification does not provide adequate written description of the claimed the genus of vaccines encoding neuroreceptor antigen, defined solely by their ability to be expressed and to raise an antibody response.

The Revised Interim Guidelines state, "when there is substantial variation with the genus, one must describe a sufficient variety of species to reflect the variation within the genus. In an

unpredictable art, adequate written description of a genus which embraces widely variant species cannot be achieved by disclosing only one species within the genus" (Column 2, page 71436, or the Revised Interim Guidelines for Written Description). Case law concurs, stating, "simply describing large genus of compounds is not sufficient to satisfy written description requirement as to particular species or sub-genus" *Fujikawa v. Wattanasin*, 39 USPQ2d 1895 (CA FC 1996). Furthermore, *Vas-Cath Inc. v. Mahurkar*, 19 USPQ2d 1111, clearly states that "applicant must convey with reasonable clarity to those skilled the art that, as of the filing date sought, he or she was in possession of the invention. The invention is, for purposes of the 'written description' inquiry, whatever is claimed." (See page 1117). The specification does not "clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is claimed." (See Vas-Cath at page 1116). Thus, the specification does not meet the written description provision of 35 U.S.C. 112, first paragraph, for genus of vaccines encoding neuroreceptor antigen, defined solely by their ability to be expressed and to raise an antibody response. Applicant is reminded that *Vas-Cath* makes clear that the written description provision of 35 U.S.C. 112 is severable from its enablement provision.

Claims 1-19 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a neurological vaccine comprising an AAV vector encoding NMDAR1 and a method of ameliorating brain damage associated with epilepsy or stroke in a rat, via prior oral administration of said vaccine, does not reasonably provide enablement for a neurological vaccine comprising any vector encoding any neuroreceptor antigen for treatment of any injury, disease or excessive neuronal activity, and a method of modulating a neurological disorder in

any subject, The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to practice the invention commensurate in scope with these claims.

The claims encompass a neurological vaccine comprising any vector encoding any neuroreceptor antigen for treatment of any injury, disease or excessive neuronal activity, and a method of modulating a neurological disorder in any subject.

The specification only discloses the use of an AAV NMDAR1 vaccine to suppress kainite-induced seizures in rats (pg. 59, Ex. 3), and to suppress stroke damage of endothelian-1 induced strokes in rats (pg. 64, Ex.4). The specification does not provide guidance on the treatment of other disease with the vaccine or the manufacture and/or use of other neurological vaccines comprising any vector encoding any neuroreceptor antigen. Finally, the specification does not provide guidance eon the administration of the vaccine via any other routes other, than oral administration.

The specification fails to provide guidance or working examples for the administration of any DNA vaccine and modification of any neurological disorder in a subject. The examples in the specification only disclose the delivery of the full length mouse NMDAR1 gene into rats, while the application recites the delivery of an antigen into a subject. Additionally, there is no guidance or working examples in the specification to indicate that if administered, the NMDAR1 vaccine induces antibodies that bind to any target receptor on a neuronal cell to directly modify the receptor or indirectly modify the function of a process involving the receptor in vivo. The specification also does not teach which specific neuronal cells the target NMDA receptor is present on. Numerous types of neuronal cells are present in the central nervous system of a

subject, such as dopaminergic neurons, serotonergic neurons, oligodendrocytes, Schwann cells, and astrocytes. The specification does not teach that the NMDAR1 receptor is expressed on all of these cells, or that by inducing antibodies to the NMDAR1 receptor, any neurological disorder can be treated.

Finally, the specification does not provide enablement for the full breadth of the claimed method of treatment for any "neurological disorder." The Specification defines a neurological disorder as any impairment or absence of a normal neurological function or presence of an abnormal neurological function in a subject (Specification, pg. 10, lines 25-32). This would include at least death (the absence of normal neurological function), insanity (impairment), and schizophrenia (abnormal function). However, the specification only provides guidance on the amelioration of brain damage in rat models of epilepsy and stroke by prior vaccination with AAV NMDAR1.

The state of the art is such that numerous problems exist in regards to administering a subunit (antigen) vaccine to humans and animals. Several characteristics of an ideal vaccine, regardless of species, must include: 1) efficacy greater than 90%, 2) effective after a single dose, 3) long lived immunity, 4) effective when given orally, and 5) high safety (Babiuk, LA. Vaccine 1 7: 1587-1595, 1999). Often, when some proteins are included in a vaccine, they may be immunosuppressive, but in other cases, the immune responses to proteins may enhance the disease (Babiuk, pg 1588, col 2). Although antigen vaccines have the advantage of increased safety, their major disadvantages are their low level of immunogenicity and rapid degradation in vivo. The rapid degradation in vivo may explain the low immunogenicity (pg 1588, col 2; pg 1590, col 2).

Additionally, the specification does not teach the timing, routes of administration, dosage, or levels of protein expression required in order to induce an antibody response of any DNA vaccine to treat any neurological disease. Further, the specification does not provide guidance on neuroreceptor antigens, other than NMDAR1 that can be targeted with a DNA vaccine in order to treat any neurological disease. The problems of DNA vaccines are analogous to those faced in the field of gene therapy. In the past the Achilles heel of gene therapy has been gene delivery, and that, most of the approaches suffer from poor efficiency of delivery and transient expression of the gene {Verma et al. (1997) Nature, Vol. 389, page 239, col. 3, pgph 2}. The difficulties in getting genes transferred efficiently to target cells and getting them expressed remained a problem at the time of filing. Pfeifer and Verma state that even "though gene therapy holds great promise for the achievement of this task, the transfer of genetic material into higher organisms still remains an enormous technical challenge {Pfeifer and Verma (2001) Annu. Rev. Genomics. Hum. Genet. 2:177-211; pg. 177, pgph 1}. Johnson-Saliba et al. concurs stating, "although thousands of patients have been involved in clinical trials for gene therapy, using hundreds of different protocols, true success has been limited. A major limitation of gene therapy approaches, especially when non-viral vectors are used, is the poor efficiency of DNA delivery." {Johnson-Saliba et al. (2001) Curr. Drug. Targets 2:371-99; Abstract}. Such problems with delivery continue to plague the field of gene therapy. Shoji et al. has characterized the current state of the art as the "tragic failure of gene therapy" because of poor delivery of gene based-medicines due to the lack of an appropriate vector that "fulfills the necessary requirements, including high transfection efficiency, non-toxicity, non-pathogenicty, non-immunogenicity, [and] non-tumorgenicity." {Shoji et al. (2004) Current Pharmaceutical Design

10 :785-796}.

The specification fails to provide guidance on any method of administration of DNA vaccine, such as an AAV encoded NMDAR1 in order to induce an immune response. The specification only teaches oral AAV vector administration (Specification pgph 60). However, the specification does not describe that administering the AAV vector by topical, intramuscular injection or direct administration can treat any neurological disease. McCluskie et al. teaches that the route of delivery of DNA vaccine influences immune responses in laboratory animals {McCluskie et al. (1999) Mol. Med. 5:287-300; Abstract}. Specifically, in one study McCluskie et al. only observed antibody responses to injected routes of administration of DNA vaccines and not to non-injected injected routes of administration of DNA vaccines, such as oral routes, sub lingual, inhalation and vaginal wall because of variation in transfection efficiency (Abstract). The specification does not provide any working examples demonstrating that any route of application of AAV encoded NMDAR1 is capable of treat any neurological disease. Furthermore, McCluskie et al. teaches that the strength and nature of the immune responses to administration of DNA vaccines varies between species and that it is not clear that results from one species are predictive in another {McCluskie et al. (1999) Molecular Medicine 5:287-300. pg 287, Abstract}.

Given the lack of guidance in the specification on the making and use of any DNA vaccine encoding any neuroreceptor antigen for the treatment of any neurological disorder and the teachings in the art, the skilled practitioner in the art would be unable to predict how to practice the invention in a manner commensurate with the scope of the claims, except as a neurological vaccine comprising an AAV vector encoding NMDAR1 and a method of

ameliorating brain damage associated with epilepsy or stroke in a rat, via prior oral administration of said vaccine, without undue and extensive experimentation.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1-19 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 1 is drawn to "excessive neuronal activity." However the specification does not clearly define what is meant by "excessive neuronal activity." The term "excessive neuronal activity" encompasses, thinking too much, manic states, as well as rapid uncontrolled firing of neurons for any reason. Therefore the metes and bounds of the claims cannot be determined. Claims 3,4,7,8,9,10 and 11 depend from claim 1

Claims 2,5,6,11, and 15-19 are drawn to any "neurological disorder." The Specification defines a "neurological disorder" as any impairment or absence of a normal neurological function or presence of an abnormal neurological function in a subject (Specification, pg. 10, lines 25-32). This encompasses any change in mental function from a normal state. However, the specification does not define what the normal baseline mental function is. Therefore the metes and bounds of the claims cannot be determined.

Claims 12 is drawn to any "neurological condition." However the specification does not clearly define what is meant by "neurological condition." The term "neurological condition"

encompasses any illness, injury or phenomena affecting the neurons. Therefore the metes and bounds of the claims cannot be determined. Claims 13-15 depend from claim 12

Claim 15 recites the limitation "neurological disorder" in claim 12. However, claim 12 does not recite a neurological disorder, it only recites a neurological condition. There is insufficient antecedent basis for this limitation in the claim.

Claim 15 recites the "genetic vaccine of claim 12". However, claim 12 is directed towards a method, not a vaccine. There is insufficient antecedent basis for this limitation in the claim.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.

Claims 1-8, 10 and 16-19 are rejected under 35 U.S.C. 102(a) as being anticipated by Lissin et al. {Lissin et al. (1998) PNAS 95:7097-7102}.

Applicant's claims are drawn to a product, such as an adenoviral vector that encodes an NMDA receptor, such as NMDAR1. However, "when the structure recited in the reference is substantially identical to that of the claims, claimed properties or functions are presumed to be inherent." See MPEP 2112.01 or In re Best, 195 USPQ 430, 433 (CCPA 1997). Further, the MPEP states that,"... in apparatus, article, and composition claims, intended use must result in a structural difference between the claimed invention and the prior art in order to patentably

distinguish the claimed invention from the prior art." In re Casey, 152 USPQ 235 (CCPA 1967); In re Otto , 136 USPQ 458, 459 (CCPA 1963)(MPEP 2111.02). The office does not have the facilities for examining and comparing applicant's product with the product of the prior art in order to establish that the product of the prior art does not possess the same material, structural and functional characteristics of the claimed product. In the absence of evidence to the contrary, the burden is upon the applicant to prove that the claimed products are functionally different than those taught by the prior art and to establish patentable differences. See Ex parte Phillips, 28 USPQ 1302, 1303 (BPAI 1993), In re Best, 562 F.2d 1252, 195 USPQ 430 (CCPA 1977) and Ex parte Gray, 10 USPQ2d 1922, 1923 (BPAI 1989).

Lissin et al. provides guidance on a an adenovirus that encodes an NMDA receptor (NR1), which is capable of being expressed in cultured hippocampal neurons (Abstract; pg. 7097, Materials and Methods). Therefore, by teaching all the limitations of the claims as written, Lissin et al. clearly anticipates the instant invention as claimed.

No claims allowed.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to (571) 272-0547. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Dr. Lou Lieto whose telephone number is (571) 272-2932. The examiner can normally be reached on Monday-Friday, 9am-5 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Dr. Ram Shukla can be reached on (571) 272-0735. The fax phone number for the organization where this application or proceeding is assigned is (571)-273-8300. Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Patent applicants with problems or questions regarding electronic images that

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